<u>IN THE UNITED STATES PATENT AND TRADEMARK OFFICE</u>

In re of Application of: O'TOOLE, MARGOT M. ET AL.
Application No.:   10,686,619   Group No.:   1634
Filed: October 17, 2003   Examiner: SALMON, KATHERINE D.
For: COMPOSITIONS AND METHODS FOR DIAGNOSING AND
                           TREATING AUTOIMMUNE DISEASE
Confirmation No.:   9490
Customer Number: 25291

Mail Stop Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

<u>DECLARATION OF MARGOT M. O'TOOLE, Ph.D. UNDER 37 C.F.R. § 1.132</u>

Sir:

I, the undersigned, Margot M. O'Toole, Ph.D., declare and state that:

1.   I am in the Biological Research Group at Wyeth within the Department of Biological Technologies and I am Team Leader for Inflammation. I received a B.A. in Biology from Brandeis University in 1973 and a Ph. D. in Immunology from Tufts University in 1979. I did Postdoctoral training at the Fox Chase Institute for Cancer Research in Philadelphia where I focused my research on the severe combined immunodeficient mouse and on transplantation antigens. I worked at the Massachusetts Institute of Technology where I was largely responsible for discovering flaws in the experimental support of idiotypic mimicry, then a theory of immunology. I joined Genetics Institute in April 1990, prior to its acquisition by Wyeth in 1996. From 1990 through 2000 I worked on the vaccine adjuvant properties of interleukin 12 and B7-IgG for both infectious disease and cancer indications. I have served on the Vaccine Adjuvant Wyeth/Genetics Institute Joint Task Force and on the Wyeth/Elan Joint Research Sub-team on Alzheimer immunotherapies. I have worked on animal models of lupus nephritis and primate models of ischemia reperfusion injury using molecular profiling to elucidate mechanisms of disease and tissue damage. In 2005 I served as a panelist for the "Standards for Safety and Efficacy Biomarkers" session of the Conference on Application and Validation of Genomic Biomarkers for Use in Drug Development and Regulatory Submissions, co-sponsored by the Drug Information Association, Food

and Drug Administration, PhRMA and the Pharmacogenomic Working Group. Wyeth has submitted nine patent applications based on my work.

2. I am an inventor in the patent application entitled "COMPOSITIONS AND METHODS FOR DIAGNOSING AND TREATING AUTOIMMUNE DISEASE." This is application number 10/686,619, filed October 17, 2003. I am familiar with the specification and claims currently pending in the above-mentioned patent application. I have read and I am familiar with the Office Action issued April 23, 2007 in the above-mentioned patent application. I understand that in the outstanding Office Action the application is rejected for lack on enablement. I understand that the Examiner has cited Kotzin (Cell, 1996, 85:303-306; referred to herein as Kotzin 1), Kotzin (J. Clin. Invest., 1997, 99:557-558; referred to herein as Kotzin 2), Liu *et al.* (Clin. Immunol., 2004, 112:225-230; referred to herein as Liu), and Morel *et al.* (PLoS Biol., 2004, 2:1061-1064; referred to herein as Morel) to conclude that "the correlation of a gene expression in mouse cannot be extrapolated to humans." (See page 10 of the Office Action.) I have read and understand these references and I would like to add my comments in response to the Office Action. In the above-mentioned patent application it was determined that the midkine gene expression was elevated in kidney samples of lupus neprhitis-affected mice (MRL/MPJ-Fas^{lpr}, MRL/MpJ, and NZB X NZW F1) when compared to controls (C57BL/6 and C57BL/6-Fas^{lpr}). The MRL/MPJ-Fas^{lpr} and NZB X NZW F1 strains of lupus neprhitis-affected mice are extensively used in the art to study lupus disease. The signs and symptoms exhibited by these mice closely parallel those observed in humans with lupus, including auto-antibody production (particularly antibodies to double stranded DNA), and glomerular nephritis leading to loss of kidney function.

3. It is my understanding that the Examiner cites Kotzin 1 and Kotzin 2 for teaching that "...an animal model may not be an accurate representation of another animal's response to lupus...[and that]...[g]enetic homology does not necessarily correlate to phenotypic expression."

4. Based on my reading of the Kotzin references, nothing in Kotzin 1 suggests a lack of correlation between elevated midkine gene expression and increased likelihood of lupus in humans. In fact, several observations of Kotzin support extrapolation of observations in mice to human disease. Specifically, Kotzin 1

teaches that animal models have contributed greatly to the elucidation of systemic lupus erythematosus pathogenesis in humans. For example, Kotzin 1 teaches identification of autoantibodies and their presence in lupus in **patients and mice**. Furthermore, Kotzin 1 states "in lupus patients **and** lupus mice, studies have repeatedly shown that a subset of anti-DNA antibody-producing B cells are clonally expanded and that their immunoglobulin genes are modified by somatic mutation." Thus, I believe that Kotzin 1 does, in fact, support extrapolation of genetic characteristics in lupus mice to humans with lupus.

5. Kotzin 2 teaches that NZB X NZW mice are "one of the best-studied models of lupus nephritis." Figure 4 of the above mentioned patent application shows that NZB X NZW F1 mice have elevated levels of midkine gene expression correlating with lupus. The signs and symptoms exhibited by NZB X NZW F1 mice closely parallel those observed in humans with lupus. Thus, contrary to the Examiner's assertions, I believe that Kotzin 2 does, in fact, support extrapolation of genetic characteristics of lupus in mice to humans with lupus.

6. It is my understanding that Liu was cited for teaching that correlation of gene expression in mice is not indicative of correlation of gene expression in humans with lupus. Liu presents expression data that is limited to NOD and NZM mouse strains. Neither of these two mouse strains is necessarily a good model of lupus nephritisbecause the NOD mouse strain is a model for diabetes and the NZM mouse strain does not necessarily develop lupus symptoms. Thus, Liu's observations in NOD and NZM mice do not refute that the results observed in the above-mentioned application may be extrapolated to humans.

7. Furthermore, I have read a report by Furukawa and Yoshimasu (Autoimmun., 2005, Rev. 4:345-350; referred to herein as Furukawa) that is referred to in the Amendment and Request for Reconsideration. Furukawa refers to the development of MRL/lpr mice, which have a mutation in the Fas gene. Furukawa states "[t]he Fas-defect is believed to accelerate the autoimmunity of MRL/lpr mice, and results in **lupus nephritis**...." Furukawa states that "[f]rom these studies, it is concluded that the lpr mutation accelerates the progression of a mild type of systemic and cutaneous connective tissue disease into a more severe one such as SLE." Thus, I

believe that Furukawa supports extrapolation of genetic characteristics in lupus mice to humans with lupus.

8. The patent application shows that one pathway that results in lupus-like symptoms involves elevation of midkine gene expression in the kidney. The data in the patent application was obtained using NZB X NZW F1 and MRL/MPJ-Fas[lpr] mice. According to Kotzin 2, NZB X NZW mice are "one of the best-studied models of lupus nephritis," and, according to Furukawa "[t]he Fas-defect is believed to accelerate the autoimmunity of MRL/lpr mice, and results in lupus nephritis...." Based on the references noted and in light of the results obtained in the present application, I believe that elevated midkine gene expression in humans correlates with lupus disease progression.

9. I hereby declare that all statements made on my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the U.S. Code and may jeopardize the validity of the application or any patent issuing therefrom.

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Margot M. O'Toole, Ph.D.

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23 - Oct - 2007
Date